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REMARKS

Claims 13-15 are pending in the instant application. Claims 13-15 are rejected. No claim is objected to. Claims 27-36 have been withdrawn as being drawn to the non-elected invention in an election mailed May 30, 2002. Claims 1-12, 16-26, 37, and 38 have been canceled and withdrawn from consideration without prejudice previously in a response mailed on November 25, 2002. Applicants reserve the right to prosecute, in one or more patent applications, the canceled claims, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. In view of the following response, Applicants believe the pending claims are allowable. Reconsideration is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

Claims 13-15 are rejected under 35 USC § 102(b) as allegedly being anticipated by Wessel, *et al.* or Fortune, *et al.* The Examiner alleges that Wessel, *et al.* disclose bisdioxopiperazine as inhibiting topoisomerase II "without stabilizing the cleaved form as a covalent complex." In addition, the Examiner alleges that Fortune, *et al.* disclose that merbarone inhibits topoisomerase II by blocking DNA cleavage.

Applicants respectfully submit that a single prior art reference anticipates a claimed invention only if it identically shows every element of the claimed invention. *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that Wessel, *et al.* and Fortune, *et al.* cannot properly anticipate the claimed invention because these references do not identically disclose the compounds recited in claims 13-15.

Claims 13 to 15 are directed to methods of modulating the activity of a mammalian type II topoisomerase enzyme comprising contacting said enzyme with a compound of formula (Ia), formula (Ib) or the selected piperadines of claim 15. Applicants respectfully submit that Wessel,

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et al. disclose inhibition of topoisomerase with a single compound, bisdioxopiperazine, which is not encompassed within the genus of compounds of the rejected claims. Similarly, Fortune, *et al.* discloses a proposed mechanism of action of inhibiting topoisomerase with merbarone, which is not encompassed within the genus of compounds of the rejected claims. Thus, neither Wessel, *et al.* nor Fortune, *et al.* disclose each and every element of claims 13-15.

Applicants respectfully submit that in view of the forgoing remarks, Applicants have overcome the Examiner's rejection under 35 U.S.C. §102(b) and that this rejection should be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

Claims 13-15 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Davies, *et al.* The Examiner alleges that Davies, *et al.* disclose compounds with the structure of formula (Ia) therein as antibacterials. The Examiner concedes that although no mechanism of action is set forth in Davies, *et al.*, the compounds are identical to those instantly claimed. The Examiner therefore alleges that such compounds "inherently inhibit the same mechanism as instantly claimed." In addition, Claims 13-15 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Coates, *et al.* and Hatton, *et al.* as also setting forth the compounds of formula (Ia). The Examiner alleges that the compounds of Coates, *et al.* and Hatton, *et al.* "inherently inhibit by the same mechanism of action as instantly claimed."

Inherent anticipation arises when "the prior art ***necessarily*** functions in accordance with, or includes, the claimed limitations," *Atlas Powder Co v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). Emphasis added. Applicants respectfully traverse these rejections for the following reasons. Davies, *et al.*, Coates, *et al.* and Hatton, *et al.* do not disclose a mechanism of action for the compounds taught by them, nor do they teach use of the compounds with mammalian topoisomerase II. In addition, a single compound may exert a different mechanism of action on

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different enzymes to which it is contacted, depending on the enzyme's physical and chemical characteristics.

Topoisomerases from different organisms vary in structure and activity. In addition, different organisms can produce and use topoisomerase II, topoisomerase IV and DNA gyrase enzymes in different ratios during DNA and cell replication. See, for example, U.S. Application No. 10/199,933. Furthermore, Applicants respectfully submit that, as is understood in the art, the structure of topoisomerases from prokaryotes is known to vary significantly from topoisomerases of eukaryotes. Mammalian cells do not produce topoisomerase IV but rather produce two isoforms of topoisomerase, which do not display gyrase activity. Type II topoisomerases of bacteria and mammalian cells are distinguished by multiple, distinct properties (Chapter 12, Kornberg and Baker, 1992, DNA Replication, 2nd edition, ISBN 0-7167-2003-5). Some of the differences between enzymes from bacteria versus mammalian cells are demonstrated by the following evidence: (1) clinically used quinolone antibacterials preferentially inhibit bacterial topoisomerases; (2) a unique characteristic of bacterial DNA gyrase is its ability to positively supercoil DNA in an ATP dependent manner (Gellert, *et al.* (1976) *Proc. Natl. Acad. Sci. USA*, (73)11:3872-3876) while human topoisomerases cannot introduce positive supercoils into DNA; (3) bacterial enzymes DNA gyrase and topoisomerase IV are A2B2 heterodimers, while human topoisomerase II is a homodimer formed from single polypeptides; (4) bacterial cells contain DNA gyrase and topoisomerase IV, both of which are essential for growth, while human cells contain isoforms of just one type II topoisomerase; and (5) ATPase activity of human and bacterial type II topoisomerases have some different characteristics (Hammonds and Maxwell, (1997) *Journal of Biological Chemistry*, (272)51:32696-32703). Copies of each of these references are provided herewith as part of an IDS.

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Furthermore, the compounds disclosed in Davies, *et al.*, Coates, *et al.*, and Hatton, *et al.* have different MIC values for the individual bacterial species against which they were tested. This fact indicates that the mechanism of action of a specific compound likely differs *even* among enzymes of different bacterial species. Therefore, the compounds disclosed in these references do not necessarily function by the same mechanism of action in each species. More importantly, neither Davies, *et al.*, Coates, *et al.*, nor Hatton, *et al.* disclose or even suggest that the compounds disclosed therein will possess the ability to modulate topoisomerase from humans. Rather, the use of the compounds disclosed in these references is only as antibacterials.

Claims 13 to 15 are directed to methods of modulating mammalian topoisomerase activity with a compound "wherein the said compound inhibits enzyme-mediated cleavage of a polynucleotide substrate." Thus, the compounds of Davies, *et al.*, Coates, *et al.*, and Hatton, *et al.* do not *necessarily* function in accordance with the claimed limitations, as they may have different mechanisms of action on mammalian topoisomerase versus bacterial.

Applicants respectfully submit that in view of the foregoing discussion, the compounds of Davies, *et al.*, Coates, *et al.*, and Hatton, *et al.* do not necessarily act via the same mechanism of action as that claimed in the present invention. Therefore, the anticipation rejection based on 102(e) cannot be maintained since the cited prior art fails to demonstrate that the compounds disclosed in that art necessarily functions in accordance with, or includes, the claimed limitations, as is required by the relevant case law.

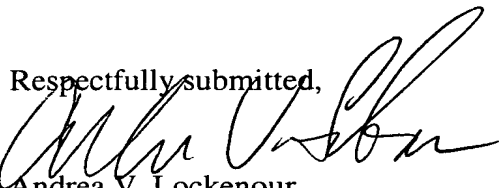
Applicants respectfully submit that in view of the forgoing remarks and the claims as amended, Applicants have overcome the Examiner's rejection under 35 U.S.C. §102(e) and that this rejection should be withdrawn.

Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the

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specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned agent.

Respectfully submitted,

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